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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/846,512 | 05/01/2001 | Rachel Meyers | MP100-185PIR2M | 5523 |

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INTELLECTUAL PROPERTY GROUP
MILLENNIUM PHARMACEUTICALS INC
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CAMBRIDGE, MA 02139

EXAMINER

YU, MISOOK

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------|---------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/846,512 | MEYERS ET AL. |
| | Examiner | Art Unit |
| | MISOOK YU, Ph.D. | 1642 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 17 February 2004.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 19,54-57,59-63 and 65-82 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 19,54-57,59-63 and 65-82 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

The amendment filed on 2/17/2004 is acknowledged. Claims 19, and 63 are amended. Claims 69-82 are new. Claims 19, 54-57, 59-63, and 82 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All of the rejection of record set forth in the Office action mailed on 10/14/2003 is rendered moot because all the rejection is based on examination of method using SEQ ID NO:12, but all of the pending claims are drawn to method using SEQ ID NO:2.

This Office action contains new grounds of rejection.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 19, 54-57, 59-63, and 65-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 19, 54-57, 59-63, and 82 are interpreted as drawn to a method using a genus of proteins related to SEQ ID NO:2 recited as 95 % homology, or 1-5 amino acid differences.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written

Description Guidelines; Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609; and Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of 95 % homology or 1-5 amino acid changes from SEQ ID NO:2. There is not even identification of function associated with the genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid molecules, given that the specification has only described SEQ ID NO: 12 and 2. Therefore, only isolated ^{protein} ~~nucleic acid~~ comprising SEQ

ID NO:12 and 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 63, and 78-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 63, and 78-82 are interpreted as drawn to method using the hydrolysis activity of the various polypeptides recited as at least 95 % SEQ ID NO:2 or 1-5 amino acid differences from SEQ ID NO:2 to determine the effect of interaction between the polypeptides and a compound. This rejection has many aspects.

First, the polypeptides must possess the enzymatic activity of hydrolyzing of a compound. The specification even fails to teach whether SEQ ID NO:2 has any hydrolysis activity, let alone the various polypeptides recited as at least 95 % SEQ ID

NO:2 or 1-5 amino acid differences from SEQ ID NO:2. The specification at page 13 states that SEQ ID NO:2 has homology to trypsin, but the specification does not teach what residues 1-5 or which 5 % amino acids could be changed to retain hydrolysis activity. One cannot extrapolate the teaching of the specification to the claims because it is well known in the art that even slight modifications in a peptide or protein structure can have significant and unpredictable effects on biological activity

Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin

binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The specification does not provide guidance as to what changes in the structure can be made retaining hydrolysis activity required for the conclusion step of the method.

Second, either Underwood et al (a copy provided with the Office action mailed on 10/14/2003, Biochim Biophys Acta. 2000 Nov 15;1502(3):337-50 or Scott et al (a copy provided with the Office action mailed on 10/14/2000, Nature Genetics, 2001, vol. 27, pages 59-63) teach that a cell (a live organism) has many proteases with hydrolysis activity. The specification does not teach how to determine whether hydrolysis of a compound is caused by SEQ ID NO:2 or any one of the other cellular proteases of a cell. Note other proteases of a cell listed in the paragraph bridging left and right columns of page 338 of Underwood et al, or the proteases produced by the alternate splicing forms disclosed at page 59 of Scott et al. In summary, neither the art nor the specification teaches an assay capable of concluding that hydrolysis of a compound is occurred by SEQ ID NO:2, polypeptides with at least 95 % SEQ ID NO:2, or polypeptides with 1-5 amino acid differences from SEQ ID NO:2.

The specification provides insufficient guidance, and provides no working examples of determine the effect of interaction between the polypeptides and a compound with hydrolysis, which would provide guidance to one skilled in the art to use and make the claimed invention without undue experimentation. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Claims 69-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This new matter rejection is made because of the new limitation "at least one but less than 5 amino acid residues from the amino acid sequence of SEQ ID NO:2" in the claims 69 and 78. Applicant states that support for the new claims are found in 09/633,300 at page 47, lines 23-28, page 48, lines 7-10, and also in 60/200,621 at page 29 lines 19-33. However, those priority documents do not have the support for the quoted limitation above. Applicant is kindly requested to point out the support the limitation in the specification as originally filed since the support is not apparent to the Office.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina C Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642



LARRY H. HELMS, PH.D
PRIMARY EXAMINER